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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

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OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: RfD/Peer Review Report of Prometon
EPA Chem Code: 080804
CAS No. 1610-18-0
Reg. Group: List B

FROM: George Z. Ghali, Ph.D. G. Ghali 9.17.92
Manager, RfD/Quality Assurance Peer Review
Health Effects Division (H7509C)

TO: Robert Taylor, PM 25
Registration Division (H7505)

Lois Rossi, Chief
Reregistration Branch
Reregistration and Special Review Division (H7508)

The Health Effects Division RfD/Peer Review Committee met on September 10, 1992 to evaluate the existing data base for Prometon and determine whether the available data are adequate for the purpose of risk assessment in accordance with the current Agency's Guidelines and Standards.

Material available for review by the Committee included an RfD summary document, data evaluation record (DER) for a chronic toxicity study in dogs, data evaluation record for a chronic toxicity/ carcinogenicity study in rats, data evaluation record for a carcinogenicity study in mice, data evaluation records for reproductive and developmental toxicity studies in rats, and data evaluation record for a developmental toxicity study in rabbits.

Prometon was first discussed by the HED RfD Committee on March 31, 1986 and an RfD was verified by the Agency on May 30, 1986 and was based upon a NOEL of 15 mg/kg/day. This was the highest dose tested in a subchronic feeding study in the rat. An uncertainty factor (UF) of 100 was used to account for interspecies extrapolation and intraspecies variability. An additional uncertainty factor of 10 was used to account for deficiencies in the data base. A preliminary limiting dose (PLD) was calculated to be 0.015 mg/kg/day.

Subsequently, additional data were submitted to the Agency and the PLD had to be revised accordingly. The RfD/Peer Review Committee recommended that an RfD be established based upon a NOEL of 0.89 mg/kg/day for decreased body weight gain and food

The Committee considered the chronic toxicity/carcinogenicity study in rats and the carcinogenicity study in mice to be acceptable and the data evaluation records for these studies to be adequate as presented.

The long-term toxicity study in dogs will remain as Core-supplementary until the additional information requested by the Agency are submitted by the registrant and evaluated by the respective branch.

The reproduction study in rats was considered acceptable and the data evaluation record for this study was considered adequate as presented. The data evaluation records for the developmental toxicity studies in rats and rabbits did not include enough information and were considered inadequate as presented. The Committee recommended reevaluation of the two studies and updating the data evaluation records. If the outcome of the reevaluation of the two studies does not confirm the conclusions as presented in the original data evaluation records of the two developmental toxicity studies, the Committee would then convene to reconsider its position on these studies.

The Committee initially classified the chemical as a Group E, based on the fact that the chemical did not demonstrate evidence for carcinogenicity in adequate studies in two animal species. However, further discussion lead the Committee to change the classification of this chemical to Group D. This shift in the Committee's position was based upon: 1) there was statistically significant increasing trend in the mammary tumor in rats, though this increase was not significant in the pair-wise comparison with the concurrent control, 2) although the increase in the tumor incidence was within the historical control range, it was at the upper end of the historical control range, 3) this type of tumor was produced in rats by some other s-triazines, and 4) lack of adequate data on mutagenicity and structure-activity relationships made it also more difficult to ascertain the "Group E" classification. In view of the above, the Committee decided to classify the chemical as a "Group D".

A. Individuals in Attendance

1. Peer Review Committee Members and Associates (signature indicates concurrence with the peer review unless otherwise stated).

William L. Burnam

Reto Engler

Marcia Van Gemert

Karl Baetcke

Henry Spencer

Gary Burin

George Ghali

Rick Whiting

2. Peer Review Members and Associates in Absentia (committee members and associates who were unable to attend the discussion; signatures indicate concurrence with the overall conclusions of the committee).

Roger Gardner

Esther Rinde —

3. Scientific Reviewer (committee or non-committee members responsible for data presentation; signatures indicate technical accuracy of panel report).

Paul Chin

CC: Penny Fenner-Crisp
Richard Schmitt
Kerry Dearfield
Esther Saito
Karl Baetcke
Marion Copley
James Kariya

C. Material Reviewed

Material available for review included an RfD summary document, data evaluation records (DER's) for a chronic toxicity study in dogs, a chronic toxicity/ carcinogenicity study in rats, a carcinogenicity study in mice, a reproductive and developmental toxicity studies in rats, and a developmental toxicity study in rabbits.

1. O'Connor, D. J., McCormick, G. C. and Green, J. D. (1988). Prometon-combined chronic toxicity/oncogenicity study in rats. Unpublished study No. 852003 conducted by Ciba-Geigy Corp., and submitted by Ciba-Geigy Agricultural Division. MRID No. 404 88102, 92149005, HED Doc. No. 009679.

Core-Classification: Core-Guideline data

Committee's conclusions and recommendations:

The Committee agreed with the reviewer's interpretation of data. The Committee agreed that the dose selection was adequate for carcinogenicity testing. This conclusion was based on mean body weight gain reduction of about 14 and 19% in males at 5 and 16 weeks respectively, and about 6 and 15% in females for the same time intervals at the highest dose tested. This study satisfies data requirement 83-1 and -2 of Subpart F of the Pesticide assessment Guideline for chronic toxicity and carcinogenicity testing in rats.

2. Osheroff, M. R. (1988). Lifetime oncogenicity study in mice with prometon. Unpublished study No. 483-234 conducted by Hazleton Laboratories, submitted by Ciba-Geigy Corporation, MRID No. 40488101, 92149009, HED Doc. No. 009679.

Core-Classification: Core-Guideline data

Committee's conclusions and recommendations:

The Committee agreed with the reviewer's interpretation of data. The Committee agreed that the dose selection was adequate for carcinogenicity testing. This conclusion was based on mean body weight gain reduction of about 33 and 24% respectively for males and females of the high dose group. The high dose tested was also considered a limit dose. This study satisfies data requirement 83-2 of Subpart F of the Pesticide assessment Guideline for carcinogenicity testing in mice.

3. Breckenridge, C. and Green, J. (1986). Prometon - one year

oral administration to dogs. Unpublished report dated December 15, 1986 prepared by Ciba - Geigy Pharmaceutical Division, submitted by Ciba - Geigy Agricultural Division, Study No. 100-84, MRID No. 40097901, 92149005, HED Doc. No. 009328.

Core-Classification:

This study was originally classified by the study reviewer as Core-minimum and then down-graded by the reviewer to a Core-supplementary.

Committee's conclusions and recommendations:

The Committee agreed with the reviewer's interpretation of data and recommended that the study should remain as Core-supplementary until all the additional information requested are received and evaluated by the respective branch. Currently, this study does not satisfy data requirement 83-1 of Subpart F of the Pesticide Assessment Guideline for chronic toxicity testing in a non-rodent species.

4. Salamom, C. M. (1987). Two-generation reproduction study in rats. Unpublished study No. 450-2208 conducted by American Biogenics Corporation, and submitted by Ciba-Geigy Corporation. MRID No. 40361501, 92149009, HED Doc. No. 009679.

Core-Classification: Core-Guideline data

Committee's conclusions and recommendations:

The Committee agreed with the reviewer's interpretation of data. This study satisfies data requirement 83-4 of Subpart F of the Pesticide assessment Guideline for reproductive toxicity testing.

5. Florek, C. Christian, M., Christian, G., et al. (1981). Teratogenicity study of prometon technical in pregnant rats. Unpublished report dated August 4, 1993 prepared by Argus Research Laboratories, study No. 203-003 submitted by Ciba-Geigy Corporation. MRID No. 00129983, 92149007, HED Doc. No. 003700, 004781.

Core-Classification: Core-minimum data

Committee's conclusions and recommendations:

The Committee considered the data evaluation record of this study to be inadequate and recommended reevaluation of the study to confirm the conclusions made in the original data evaluation records. A complete new data evaluation records may not be necessary, an addendum attached to the original data evaluation

records will be sufficient. Classification of this study will be reserved until the study is reevaluated. This study, at this time, does not satisfy data requirement 83-3 of Subpart F of the Pesticide Assessment Guideline.

6. **Lightkep, G., Christian, M., Christian, G., et al. (1982). Teratogenic potential of prometon technical in New Zealand white rabbits. Unpublished report dated August 4, 1993 prepared by Argus Research Laboratories, study No. 203-002 submitted by Ciba-Geigy Corporation. MRID No. 00129984, 92149008, HED Doc. No. 003700, 004781.**

Core-Classification: Core-minimum data

Committee's conclusions and recommendations:

The Committee considered the data evaluation record of this study to be inadequate and recommended reevaluation of the study to confirm the conclusions made in the original data evaluation records. A complete new data evaluation records may not be necessary, an addendum attached to the original data evaluation records will be sufficient. The classification of this study will be reserved until the study is reevaluated. This study, at this time, does not satisfy data requirement 83-3 of Subpart F of the Pesticide Assessment Guideline.

D. Reference Dose

The RfD/Peer Review Committee recommended that an RfD be established based upon a NOEL of 0.89 mg/kg/day for decreased body weight gain and food consumption observed at 23.3 mg/kg/day in a two-year feeding/carcinogenicity study in rats using a UF of 100 to account for the interspecies extrapolation and intraspecies variability.

E. Carcinogenicity Classification

The Committee initially classified the chemical as a Group E, based on the fact that the chemical did not demonstrate evidence for carcinogenicity in adequate studies in two animal species. However, further discussion lead the Committee to change the classification of this chemical to Group D. This shift in the Committee's position was based upon: 1) there was a statistically significant increasing trend in the incidence of mammary tumors in rats, though this increase was not significant in the pair-wise comparison with the concurrent control, 2) although the increase in the tumor incidence was within the historical control range, it was

at the upper end of the historical control range, 3) this type of tumor was produced in rats by some other s-triazine, and 4) lack of adequate data on mutagenicity and structure-activity relationship made it also more difficult to ascertain the "Group E" classification. In view of the above, the Committee decided to classify the chemical as a "Group D".

F. Referral To Other Committees

No referral has been made to the carcinogenicity or developmental/reproductive toxicity peer review committees at this time.

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PC Code:	**080804**
HED File Code	**21200 PEER REVIEW**
Memo Date:	**11/25/92 12:00:00 AM**
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